

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Robert K. Naviaux Art Unit: 1614
Application No.: 09/889,251 Examiner: P. Spivack
Filed: November 1, 2001
Title: METHODS OF TREATMENT OF MITOCHONDRIAL DISORDERS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION OF
APPLICANT UNDER 37 C.F.R. § 1.131

Sir:

I, Robert K. Naviaux, inventor of the above-identified application, do hereby declare and state that:

1. I am familiar with the above-identified patent application and the disclosure in the specification of methods for treating various disorders.
2. I have reviewed the Office Action mailed September 9, 2004, and I understand that claims 68 and 92 have been rejected, *inter alia*, under 35 U.S.C. § 102(a), as allegedly being anticipated by Loffler et al., Dihydroorotat-Ubiquinone Oxidoreductase Links Mitochondria In the Biosynthesis Of Pyrimidine Nucleotides, *Molecular and Cellular Biochemistry*, 174: 125-129 (1997). I further understand that Claims 67-80 and 88-94 have been rejected, *inter alia*, under 35 U.S.C. § 103(a), as allegedly being obvious over U.S. Patent No. 6,472,378 to von Borstel. I understand that the filing date of the von Borstel patent is August 31, 1998.
3. Prior to the publication date of Loffler et al. and the priority date of von Borstel, I had used the methods disclosed in the above-identified application. Particularly, I used uridine to achieve effective treatment of various mitochondrial disorders. Therefore, I conceived of and

reduced to practice the methods claimed in the current application before the publication of the Loffler paper and before the priority date of the von Borstel patent. This can be evidenced by entries in my laboratory book. A copy of pertinent pages is attached herewith as Exhibit A. This can be also corroborated by the declaration of Dr. William Nyhan which is attached herewith as Exhibit B.

4. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

3/3/05
Date

R. K. Naviaux
Robert K. Naviaux

STARTED URIDINE

1 WEEK INTO URIDINE 2g TID

↑ vocalization

"unintelligible sentences-like vocalization"

Ø

ATTEMPT TO JUMP - ARMS RAISED OVER HEAD
WHEN ASKED.

GAIT



NOW NORMAL. WERE THESE TO
BEFORE?

HAPPILY RUNS ROUND

BROAD-BASED, ATAXIC GAIT.

~10"

⇒ CHECK INTO EMPLOYEE CLASS PRIVILEGES
START TRIACETYURIDINE IF URIDINE WORKS

2g AC N G TID X 3 wks

5g AC N G TID X 1 wk

52" 7AM

6AM

9AM

Better appetite
Holding Sippy Cup

TEGRETOL THROUGH 9.1

LANGUAGE "MAMA", later more vocal
"Sing" day - "Seems street"

↑ fine motor @ Dy case
Better attention span
Better persistence to accomplish tasks

Balance improved - falling less
Breaks at waist
Goes up & down stairs on her own

HC 50cm

Hepatitis B (C)

Nail Mating T cell receptors

GINOY FIBROBLASTS
MIKE BLANKET

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Application No.: 09/889,251 Examiner: P. Spivack
Filed: November 1, 2001 Confirmation No. 9760
Title: METHODS OF TREATMENT OF MITOCHONDRIAL DISORDERS

DECLARATION BY DR. WILLIAM L. NYHAN

I, William L. Nyhan, MD, Ph.D., am a professor of pediatrics with the School of Medicine, University of California at San Diego, where I am also a practicing physician (CV attached). I do hereby declare and state that:

1. I am familiar with the mitochondrial diseases and disorders that are proposed to be treated using the methods provided in the above-identified patent application. I have been treating patients having such disorders for many years.

2. I have reviewed claims that are pending in the above-identified application and understand that the claims are directed to methods for treating various mitochondrial diseases and disorders using uridine. I understand that the methods of treatment are generally encompassed in independent claims 67 and 91, and particular mitochondrial diseases and disorders to be treated are described in some of the dependent claims.

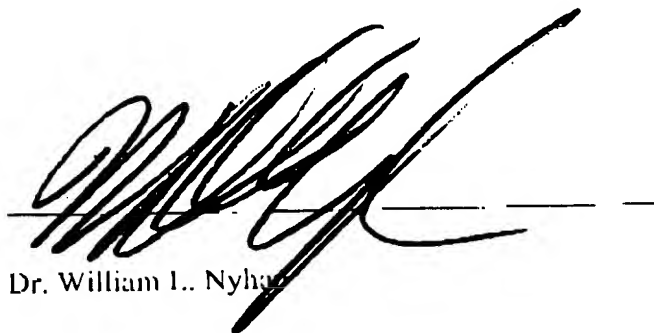
3. I first became aware of the fact that Dr. Naviaux suggested the idea of using uridine for treating various mitochondrial diseases and disorders in 1995. Both Dr. Naviaux and I attended "1995 Mitochondrial Diseases Symposium" held at Indianapolis, Indiana between June 30 and July 2, 1995. During one of our conversations in Indianapolis, Dr. Naviaux told me that he had learned that uridine is an important compound in the electron chain transport.

4. This discussion with Dr. Naviaux is very memorable to me for a number of reasons. First, the idea of using uridine had impressed me as a brilliant idea. Second, Dr. Naviaux is a colleague who also works at UCSD. For that reason, in 1995 I was in almost daily contact with Dr. Naviaux but had not heard about his idea of treatment using uridine previously.

5. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

3/2/05

Date



Dr. William L. Nyhan